Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Melphalan Flufenamide (multiple myeloma (after at least 3 prior therapies, combination with dexamethasone))

of 16 March 2023

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient melphalan flufenamide on 1 October 2022 in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 30 September 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 January 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of melphalan flufenamide compared with the appropriate comparator therapy could be determined on the basis of the

dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of melphalan flufenamide.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Melphalan Flufenamide (Pepaxti) in accordance with the product information

Pepaxti is indicated, in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy. For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation.

Therapeutic indication of the resolution (resolution of 16 March 2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy; the time to progression at least three years for subjects with prior autologous stem cell transplantation

Appropriate comparator therapy for melphalan flufenamide in combination with dexamethasone:

A patient-individual therapy under selection of:

- Bortezomib monotherapy
- Bortezomib + pegylated liposomal doxorubicin
- Bortezomib + dexamethasone

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

- Carfilzomib + lenalidomide and dexamethasone
- Carfilzomib + dexamethasone
- Daratumumab + lenalidomide + dexamethasone
- Daratumumab + bortezomib + dexamethasone
- Daratumumab monotherapy (only for subjects with disease progression on last therapy)
- Daratumumab + pomalidomide + dexamethasone
- Elotuzumab + lenalidomide + dexamethasone
- Elotuzumab + pomalidomide + dexamethasone (only for subjects with disease progression on last therapy)
- Isatuximab + pomalidomide + dexamethasone (only for subjects with disease progression on the last therapy)
- Ixazomib + lenalidomide + dexamethasone
- Lenalidomide + dexamethasone
- Panobinostat + bortezomib and dexamethasone
- Pomalidomide + bortezomib and dexamethasone
- Pomalidomide + dexamethasone (only for subjects with disease progression on the last therapy)
- Cyclophosphamide (in combination with other antineoplastic medicinal products)
- Melphalan
- Doxorubicin
- Carmustine (in combination with other cytostatic agents and a corticosteroid, especially prednisone)
- Vincristine
- Dexamethasone
- Prednisolone
- Prednisone
- Best supportive care

taking into account prior therapies as well as the extent and duration of the response.

<u>Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:</u>

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.

2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In addition to melphalan flufenamide, the following active ingredients are approved for the present therapeutic indication:

Belantamab mafodotin, bortezomib, carfilzomib, carmustine, ciltacabtagene autoleucel, cyclophosphamide, daratumumab, dexamethasone, doxorubicin, doxorubicin (pegylated liposomal), elotuzumab, idecabtagen vicleucel, isatuximab, ixazomib, lenalidomide, melphalan, panobinostat, pomalidomide, prednisolone, prednisone, selinexor, teclistamab[2] and vincristine.

The marketing authorisations are in part linked to (specified) concomitant active ingredients and to the type of the prior therapies.

on 2. It is assumed that high-dose chemotherapy with stem cell transplant is not an option for patients at the time of current therapy. Therefore, a non-medicinal treatment cannot be considered in the present therapeutic indication.

on 3. Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V:

- Idecabtagen vicleucel – resolution of 16 June 2022
- Belantamab mafodotin – resolution of 4 March 2021
- Carfilzomib – resolutions of 15 February 2018 and 15 July 2021
- Daratumumab – resolutions of 15 February 2018, 3 February 2022 and 15 September 2022
- Elotuzumab – resolutions of 1 December 2016 and 16 December 2021
- Isatuximab – resolutions of 4 November 2021
- Ixazomib – resolution of 21 April 2022
- Panobinostat – resolution of 17 March 2016
- Pomalidomide – resolutions of 17 March 2016 and 5 December 2019

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the

[2] Currently unavailable in Germany.

comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V.

Among the approved active ingredients listed under 1.), only certain active ingredients named below will be included in the appropriate comparator therapy, taking into account the evidence on therapeutic benefit, the guideline recommendations and the reality of health care provision.

The evidence is limited for patients who have received at least three lines of prior therapy. A uniform treatment standard cannot be derived from the available evidence. National and international guidelines generally refer to patient-individual therapy, which is influenced by various factors. According to the S3 guideline, the response and tolerability of prior myeloma therapy play a key role in the choice of therapy.

With regard to the relapsed disease situation, the S3 guideline initially states that a triplet therapy with two new substances (monoclonal antibody, immunomodulatory agent, proteasome inhibitor) and a steroid should be used for patients in the first relapse. Furthermore, with reference to the respective approved therapeutic indications of the active ingredients, the guideline on the therapy of the 1st to 3rd relapse states that regarding each combination therapy all product classes are generally used and combined in individual order. This is also done against the background that a therapeutic advantage of triplet therapies over doublet therapies is countered by an increased therapy toxicity, so that they are unsuitable for all patients. According to the S3 guideline, patients with 4 or more prior therapies should be examined to see whether a triplet therapy is reasonable and possible. Furthermore, there is a recommendation that a therapy with classical cytostatic agents should also be examined.

With regard to the treatment setting with at least three prior therapies, the scientific-medical societies focus on a heterogeneous patient collective. It also follows that an individual therapy has to be chosen for the treatment setting, which is determined by patient-related factors, whereby the prior therapies and the response to them also play an important role here. If the patients showed an adequate and long response to a therapy, a re-therapy can in principle also be considered according to the scientific-medical societies. Immunomodulating substances or proteasome inhibitors can also be used again in later lines of therapy, whereby another preparation of these substance classes should be used preferentially. In addition to combination therapies with novel active ingredients, the scientific-medical societies also refer to classical cytostatic agents.

Overall, all approved active ingredients and combinations of active ingredients thereof can be considered.

For isatuximab in combination with carfilzomib and dexamethasone, the benefit assessment of the G-BA did not show an additional benefit compared to carfilzomib in combination with dexamethasone (resolution of 4 November 2021). The same applies to carfilzomib in combination with daratumumab and dexamethasone, according to which an additional benefit compared to carfilzomib in combination with dexamethasone is not proven (resolution of the G-BA of 15 July 2021). For idecabtagen

vicleucel, a hint for a non-quantifiable additional benefit was established by resolution of the G-BA of 16 June 2022 because the scientific data basis did not allow quantification. This was done against the background that no statement could be made about the extent of the additional benefit on the basis of the indirect comparisons presented. The active ingredients or combinations of active ingredients mentioned cannot be considered as an appropriate comparator therapy for the present resolution.

Belantamab mafodotin as monotherapy is only indicated after at least four prior therapies, according to its authorisation status and the available evidence, which means that there is a relevant difference with regard to the treatment setting compared to subjects who have received at least three prior therapies. Therefore, belantamab mafodotin is not considered as an appropriate comparator therapy.

The active ingredient selinexor is a new treatment option for the treatment setting after at least one prior therapy (combination with bortezomib and dexamethasone) and at least four prior therapies (combination with dexamethasone). The active ingredient was approved on 26.03.2021 and has only been available in Germany for a short time. Based on the generally accepted state of medical knowledge, selinexor is not determined to be an appropriate comparator therapy for the present resolution.

The active ingredient ciltacabtagene autoleucel is also a new treatment option for the treatment setting after at least three prior therapies. The active ingredient was approved on 25.05.2022 and has only been available in Germany for a short time. Based on the generally accepted state of medical knowledge, ciltacabtagene autoleucel is not determined to be an appropriate comparator therapy for the present resolution.

In accordance with the recommendation of the S3 guideline, the G-BA also assumes that no further antineoplastic/myeloma-specific therapy can be considered for some patients, best supportive care being the appropriate treatment for them. Best supportive care is defined as the therapy that provides the best possible, patient-individual, optimised supportive treatment to alleviate symptoms and improve quality of life.

Overall, the appropriate comparator therapy is therefore a patient-individual therapy with selection of:

- Bortezomib monotherapy
- Bortezomib + pegylated liposomal doxorubicin
- Bortezomib + dexamethasone
- Carfilzomib + lenalidomide and dexamethasone
- Carfilzomib + dexamethasone
- Daratumumab + lenalidomide + dexamethasone
- Daratumumab + bortezomib + dexamethasone
- Daratumumab monotherapy (only for subjects with disease progression on last therapy)
- Daratumumab + pomalidomide + dexamethasone
- Elotuzumab + lenalidomide + dexamethasone

- Elotuzumab + pomalidomide + dexamethasone (only for subjects with disease progression on last therapy)
- Isatuximab + pomalidomide + dexamethasone (only for subjects with disease progression on the last therapy)
- Ixazomib + lenalidomide + dexamethasone
- Lenalidomide + dexamethasone
- Panobinostat + bortezomib and dexamethasone
- Pomalidomide + bortezomib and dexamethasone
- Pomalidomide + dexamethasone (only for subjects with disease progression on the last therapy)
- Cyclophosphamide (in combination with other antineoplastic medicinal products)
- Melphalan
- Doxorubicin
- Carmustine (in combination with other cytostatic agents and a corticosteroid, especially prednisone)
- Vincristine
- Dexamethasone
- Prednisolone
- Prednisone
- Best supportive care

taking into account prior therapies as well as the extent and duration of the response.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment order.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

Change of the appropriate comparator therapy

Originally, the therapy options included in the patient-individual therapy determined as the appropriate comparator therapy did not include the combination therapy "daratumumab in combination with pomalidomide and dexamethasone".

The present resolution adds the combination therapy "daratumumab in combination with pomalidomide and dexamethasone" to the selection of therapy options in the context of patient-individual therapy.

The statements of the clinical experts in the present benefit assessment procedure also showed that in the present treatment setting in everyday clinical practice, the combination therapy pomalidomide + dexamethasone is often extended by another concomitant active

ingredient in the sense of a triplet therapy. According to clinical experts, monoclonal antibodies in particular can be added.

By resolution of the G-BA of 3 February 2022, a hint for a minor additional benefit was identified for daratumumab in combination with pomalidomide and dexamethasone for the patient group of patients with at least two prior therapies and disease progression on the last therapy compared to pomalidomide in combination with dexamethasone.

Taking into account the statements of the clinical experts, "daratumumab in combination with pomalidomide and dexamethasone" is added to the selection of therapy options within the scope of the patient-individual therapy determined as the appropriate comparator therapy.

This change to the appropriate comparator therapy has no effects on the present assessment of the additional benefit, nor does it require the benefit assessment to be carried out again.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of melphalan flufenamide in combination with dexamethasone is assessed as follows:

An additional benefit is not proven.

Justification:

Data basis

For the proof of an additional benefit of melphalan flufenamide in combination with dexamethasone, the pharmaceutical company presented the results from a sub-population of the OCEAN study. In addition, the pharmaceutical company presented results from a sub-population of the HORIZON study.

OCEAN study

The randomised, open-label, controlled phase III OCEAN study compared treatment with melphalan flufenamide in combination with dexamethasone to combination therapy of pomalidomide and dexamethasone (Pd). The study enrolled patients with relapsed, refractory multiple myeloma who had previously received two to four prior lines of therapy, including both lenalidomide and a proteasome inhibitor. They had to be either refractory or relapsed and refractory to the last line of therapy and to lenalidomide within the last 18 months before randomisation and have shown disease progression on or after the last therapy. Patients with primary refractory disease and those who had already received pretreatment with pomalidomide were excluded.

A total of 495 patients were randomised in a 1:1 ratio into the two treatment arms of the study (N = 246 melphalan flufenamide; N = 249 Pd). Randomisation was stratified by age (≥ 75 years vs < 75 years), number of prior lines of therapy (2 vs 3 to 4), and International Staging System (ISS) stage (I vs ≥ II).

Treatment continued in both arms until occurrence of a reason for discontinuation such as disease progression, unacceptable toxicity or withdrawal of consent.

OCEAN is conducted at 108 study sites in Europe, North America and Asia. The study was launched in June 2017 and is currently ongoing.

In the dossier for the benefit assessment, a sub-population of the OCEAN study tailored to the target population of melphalan flufenamide in combination with dexamethasone was submitted by the pharmaceutical company. This was done against the background that the

inclusion criteria of the OCEAN study with regard to the prior therapies of the patients are in part broader or narrower than the specifications for the use of melphalan flufenamide in combination with dexamethasone or of Pd according to the product information. According to the pharmaceutical company, the submitted sub-population comprises adult patients with multiple myeloma who have received at least three prior lines of therapy, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent and one CD38 monoclonal antibody, and who have shown disease progression on or after the last therapy. In patients with previous autologous stem cell transplantation, the time to progression after transplantation should be at least 3 years. The sub-population presented comprises a total of 22 patients (12 in the intervention arm; 10 in the comparator arm).

For the benefit assessment, the data cut-off of 03.02.2021 was submitted for the described sub-population of the OCEAN study, which represents the final analysis for the endpoint PFS and the final data cut-off of the study.

Furthermore, for the endpoint of overall survival, additional analyses were submitted for a follow-up from 03.02.2022, which, however, do not refer to the sub-population tailored for the benefit assessment. According to the pharmaceutical company, the above-mentioned analysis had been prepared at the request of the EMA.

HORIZON study

The single-arm, open-label phase II HORIZON study of melphalan flufenamide in combination with dexamethasone enrolled patients with relapsed, refractory multiple myeloma who had received at least two prior lines of therapy, including an immunomodulatory agent and a proteasome inhibitor. They had to have been refractory to pomalidomide and/or a CD38 monoclonal antibody.

In the benefit assessment dossier, the pharmaceutical company presents the results of the sub-population of patients who were triple refractory or intolerant to at least one immunomodulatory agent, one proteasome inhibitor and one CD38 monoclonal antibody.

Assessment

On the relevance of the OCEAN study

In the OCEAN study, all patients in the comparator arm received a uniform treatment regimen of Pd. In contrast, the G-BA determined the appropriate comparator therapy for the present assessment to be a patient-individual therapy, which provides for a selection from a number of different treatment regimens, taking into account the prior therapies as well as the characteristics and duration of the response in the sense of a multi-comparator study. According to IQWiG's dossier assessment, the data presented for the OCEAN study were not assessed as suitable for the benefit assessment against this background.

Irrespective of the question of the extent to which the comparator pomalidomide + dexamethasone could have been considered for some of the patients, the G-BA points out that, according to IQWiG's dossier assessment, neither advantages nor disadvantages of melphalan flufenamide in combination with dexamethasone were shown in the presented results from the tailored sub-population of the OCEAN study. In addition, the number of patients in the sub-population presented is small as it comprises only 22 patients out of the total of 495 patients enrolled in the OCEAN study.

Against this background, the results presented from the OCEAN study are unsuitable for the proof of an additional benefit of melphalan flufenamide in combination with dexamethasone compared to the appropriate comparator therapy within the scope of the present assessment.

On the relevance of the HORIZON study

As no conclusions on the additional benefit of melphalan flufenamide in combination with dexamethasone compared to the appropriate comparator therapy can be derived due to the lack of a comparator arm in the HORIZON study, the presented results of the HORIZON study are not used for the present assessment.

Conclusion

Therefore, there are no suitable data to demonstrate an additional benefit of melphalan flufenamide in combination with dexamethasone compared to the appropriate comparator therapy. Thus, an additional benefit of melphalan flufenamide in combination with dexamethasone is not proven.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Pepaxti with the active ingredient melphalan flufenamide.

Melphalan flufenamide is indicated, in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy. For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation.

A patient-individual therapy was determined to be the appropriate comparator therapy, taking into account the prior therapies as well as the extent and duration of the response. Various combination therapies and monotherapies were determined as comparators for the patient-individual therapy. This includes a choice of treatment options approved for multiple myeloma as well as best supportive care.

The pharmaceutical company presents the results from a sub-population of 22 patients tailored to the target population of melphalan flufenamide in the OCEAN study, an open-label, controlled phase III study comparing melphalan flufenamide in combination with dexamethasone (Md) versus pomalidomide in combination with dexamethasone (Pd). In addition, it presents the results from a sub-population of the single-arm, open-label phase II study HORIZON.

In the OCEAN study, all patients in the comparator arm received a uniform treatment regimen of Pd. In contrast, the G-BA determined the appropriate comparator therapy to be a patient-individual therapy, which provides for a selection from a number of different treatment regimens, taking into account the prior therapies as well as the severity and duration of the response in the sense of a multi-comparator study. Irrespective of the question of the extent to which the comparator Pd could have been considered for some of the patients, the G-BA points out that neither advantages nor disadvantages of Md were shown in the results presented for the tailored sub-population. The number of patients in the sub-population presented is also small, only 22 out of a total of 495. The results presented from the OCEAN

study are unsuitable for demonstrating an additional benefit of Md compared to the appropriate comparator therapy.

Due to the lack of a comparator arm, the results of the HORIZON study are not used for the present assessment.

Due to the lack of suitable data to demonstrate an additional benefit of melphalan flufenamide in combination with dexamethasone compared with the appropriate comparator therapy, an additional benefit of melphalan flufenamide in combination with dexamethasone is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

With regard to the data submitted by the pharmaceutical company in the dossier for the benefit assessment, an overall overestimation of the number of patients can be assumed. This is based in particular on the fact that the calculation lacks a limitation to patients who show disease progression. Furthermore, the pharmaceutical company makes the implicit assumption that the disease of those patients is refractory to at least one proteasome inhibitor, one immunomodulatory agent and one anti-CD38 monoclonal antibody who have each received at least one prescription for these substance classes. This also results in an overestimation of the number of patients.

Against this background, the resolution is based on the number of patients from the last resolution on multiple myeloma after at least three prior lines of therapy (idecabtagen vicleucel (16 June 2022)). It should be taken into account that the corresponding data refer to a slightly different indication. The respective therapeutic indications differ with regard to the required melphalan flufenamide refractoriness of the disease to certain product classes and further limitation of patients with previous autologous SCT without progression within 3 years after transplantation. Despite the correspondingly narrower therapeutic indication of melphalan flufenamide, the figures presented by the pharmaceutical company in the dossier for the benefit assessment are higher than the figures from the resolution on idecabtagen vicleucel. Thus, the latter are assumed to be the better estimate and are used as the basis for the present resolution. With regard to these underlying figures, it is noted that they are to be regarded as a value in the range of a maximum order of magnitude in the present therapeutic indication.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Pepaxti (active ingredient: melphalan flufenamide) at the following publicly accessible link (last access: 12 December 2022):

https://www.ema.europa.eu/en/documents/product-information/pepaxti-epar-product-information_en.pdf

Treatment with melphalan flufenamide should only be initiated and monitored by specialists in internal medicine, haematology and oncology experienced in the treatment of patients with multiple myeloma.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 March 2023).

The costs for the first year of treatment are shown for the cost representation in the resolution.

Best supportive care:

The treatment costs for best supportive care are different for each individual patient. Because best supportive care has been determined as the appropriate comparator as part of a patient-individual therapy, best supportive care is also reflected in the medicinal product to be assessed. The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and the maximum treatment duration, if specified in the product information.

For bortezomib monotherapy and in combination with pegylated liposomal doxorubicin, a treatment duration of eight cycles is assumed, even if the actual treatment duration may differ from patient to patient.

Treatment with ixazomib in combination with lenalidomide and dexamethasone for more than 24 cycles should be based on an individual risk-benefit assessment, as data on tolerability and toxicity beyond 24 cycles are limited.

The maximum cumulative total dose of doxorubicin is 450 - 550 mg/m^2 BSA. On this basis, an approximate treatment duration of 6 to 9 cycles is used for monotherapy with doxorubicin.

The costs incurred for prednisone and prednisolone cannot be precisely quantified due to the largely lacking dosage data in the relevant therapeutic indication.

The cost representation for the active ingredient dexamethasone as a suitable comparator in the context of a patient-individual therapy is made with reference to the treatment regimen used in the MM-003 study.[3]

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Melphalan flufenamide in combination with dexamethasone				
Melphalan flufenamide	Continuously, 1 x every 28 days	13.0	1	13.0
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13.0	4	52.0
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Bortezomib monotherapy				
Bortezomib	Day 1, 4, 8, 11 21-day cycle	8.0	4	32.0
Bortezomib in combination with pegylated liposomal doxorubicin				
Bortezomib	Day 1, 4, 8, 11 21-day cycle	8.0	4	32.0
Doxorubicin (pegylated, lysosomal)	Day 4 21-day cycle	8.0	1	8.0
Bortezomib in combination with dexamethasone				
Bortezomib	Day 1, 4, 8, 11 21-day cycle	4.0 - 8.0	4	16.0 - 32.0
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 21-day cycle	4.0 - 8.0	8	32.0 - 64.0
Carfilzomib in combination with lenalidomide and dexamethasone				
Carfilzomib	1st -12th cycle Day 1, 2, 8, 9, 15, 16	13.0	1st - 12th cycle	1st year 76.0

[3] Miguel JS, Weisel K, Moreau P et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013 Oct;14(11):1055-1066. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(13)70380-2/fulltext

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	From 13th cycle Day 1, 2, 15, 16 28-day cycle		6	
Lenalidomide	Day 1 - 21 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13.0	4	52.0
Carfilzomib in combination with dexamethasone				
Carfilzomib	Day 1, 2, 8, 9, 15, 16 28-day cycle	13.0	6	78.0
Dexamethasone	Day 1, 2, 8, 9, 15, 16, 22, 23 28-day cycle	13.0	8	104.0
Daratumumab in combination with lenalidomide and dexamethasone				
Daratumumab	Week 1 - 8: 1 x every 7 days Week 9 - 24: 1 x every 14 days From week 25: 1 x every 28 days	1st year: 23.0	1	1st year 23.0
Lenalidomide	Day 1 - 21 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13.0	1st year 0 (cycle 1 - 2) 2 (cycle 3 - 6) 3 (from cycle 7)	1st year 29.0[4]
Daratumumab in combination with bortezomib and dexamethasone				
Daratumumab	Week 1 - 9 1 x every 7 days Week 10 - 24 1 x every 21 days From week 25 1 x every 28 days	1st year 21.0	1	1st year 21.0

[4] On the days of daratumumab administration, 20 mg of the dexamethasone dose is used as premedication and 20 mg on the day after daratumumab administration

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Bortezomib	Day 1, 4, 8 and 11 21-day cycle	8.0	4	32.0
Dexamethasone	Day 1, 2, 4, 5, 8, 9, 11, 12 of the bortezomib cycles	8.0	6 (cycle 1 - 3) 7 (cycle 4 - 8)	53.0[4]
Daratumumab monotherapy (only for subjects with disease progression on last therapy)				
Daratumumab	Week 1 - 8: 1 x every 7 days Week 9 - 24: 1 x every 14 days From week 25: 1 x every 28 days	1st year: 23.0	1	1st year 23.0
Elotuzumab in combination with lenalidomide and dexamethasone				
Elotuzumab	1st - 2nd cycle Day 1, 8, 15, 22 From 3rd cycle Day 1, 15 28-day cycle	13.0	1st - 2nd cycle 4 From 3rd cycle 2	1st year 30.0
Lenalidomide	Day 1 - 21 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13.0	4	52.0
Elotuzumab + pomalidomide + dexamethasone (only for subjects with disease progression on last therapy)				
Elotuzumab	1st - 2nd cycle Day 1, 8, 15, 22 From 3rd cycle Day 1 28-day cycle	13.0	1st - 2nd cycle 4 From 3rd cycle 1	1st year 19.0
Pomalidomide	Day 1 - 21 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13.0	4	52.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Isatuximab in combination with pomalidomide and dexamethasone (only for subjects with disease progression on last therapy)				
Isatuximab	1st cycle Day 1, 8, 15, 22 From 2nd cycle Day 1, 15 28-day cycle	13.0	1st cycle 4 From 2nd cycle 2	1st year 28.0
Pomalidomide	Day 1 - 21 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13.0	1st cycle 0 From 2nd cycle 2	1st year 24.0
Ixazomib in combination with lenalidomide and dexamethasone				
Ixazomib	Day 1, 8, 15 of a 28-day cycle	13.0	3	39.0
Lenalidomide	Day 1 - 21 of a 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15 and 22 of a 28-day cycle	13.0	4	52.0
Lenalidomide in combination with dexamethasone				
Lenalidomide	Day 1 - 21 28-day cycle	13.0	21	273.0
Dexamethasone	1st - 4th cycle Day 1 - 4, 9 - 12, 17 - 20 From 5th cycle Day 1 - 4 28-day cycle	13.0	1st - 4th cycle 12 From 5th cycle 4	1st year 84.0
Panobinostat in combination with bortezomib and dexamethasone				
Panobinostat	1st - 16th cycle Day 1, 3, 5, 8, 10, 12 21-day cycle	8.0 - 16.0	6	48.0 - 96.0
Bortezomib	1st - 8th cycle Day 1, 4, 8, 11	8.0 - 16.0	1st - 8th cycle:	32.0 - 48.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	9th - 16th cycle Day 1, 8 21-day cycle		4 9th - 16th cycle: 2	
Dexamethasone	1st - 8th cycle Day 1, 2, 4, 5, 8, 9, 11, 12 9th - 16th cycle Day 1, 2, 8, 9 21-day cycle	8.0 - 16.0	1st - 8th cycle: 8 9th - 16th cycle: 4	64.0 - 96.0
Pomalidomide in combination with bortezomib and dexamethasone				
Pomalidomide	Day 1 - 14 21-day cycle	17.4	14	243.6
Bortezomib	1st - 8th cycle Day 1, 4, 8, 11 From 9th cycle Day 1, 8 21-day cycle	17.4	1st - 8th cycle 4 From 9th cycle 2	1st year 50.8
Dexamethasone	1st - 8th cycle Day 1, 2, 4, 5, 8, 9, 11, 12 From 9th cycle Day 1, 2, 8, 9 21-day cycle	17.4	1st - 8th cycle 8 From 9th cycle 4	1st year 101.6
Pomalidomide in combination with dexamethasone (only for subjects with disease progression on last therapy)				
Pomalidomide	Day 1 - 21 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13.0	4	52.0
Cyclophosphamide (in combination with other antineoplastic medicinal products) [6]				
Cyclophosphamide	Day 1 35-day cycle	10.4	1	10.4
Melphalan	Day 1 - 4	10.4	4	41.6

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	35-day cycle			
Carmustine	Day 1 35-day cycle	10.4	1	10.4
Vincristine	Day 1 35-day cycle	10.4	1	10.4
Prednisone	1st - 3rd cycle Day 1 - 7, 8 - 14 From 4th cycle Day 1 - 7	10.4	1st - 3rd cycle 14 From 4th cycle 7	1st year 93.8
Melphalan				
Melphalan	Continuously, 1 x every 28 days	13.0	1	13.0
Doxorubicin				
Doxorubicin	Day 1 21-day cycle	6.0 - 9.0	1	6.0 - 9.0
Carmustine (in combination with other cytostatic agents and a corticosteroid, especially prednisone)				
Carmustine	Day 1 35-day cycle	10.4	1	10.4
Cyclophosphamide	Day 1 35-day cycle	10.4	1	10.4
Melphalan	Day 1 - 4 35-day cycle	10.4	4	41.6
Vincristine	Day 1 35-day cycle	10.4	1	10.4
Prednisone	1st - 3rd cycle Day 1 - 7, 8 - 14 From 4th cycle Day 1 - 7	10.4	1st - 3rd cycle 14 From 4th cycle 7	1st year 93.8
Vincristine				
Vincristine	Continuously, 1 x every 7 days	52.1	1	52.1
Dexamethasone				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Dexamethasone [3]	Day 1-4, 9-12 and 17-20 28-day cycle	13.0	12	156.0
Daratumumab in combination with pomalidomide and dexamethasone				
Daratumumab	Week 1 - 8: 1 x every 7 days Week 9 - 24: 1 x every 14 days From week 25: 1 x every 28 days	1st year: 23.0	1	1st year 23.0
Pomalidomide	Day 1 - 21 28-day cycle	13.0	21	273.0
Dexamethasone	Day 1, 8, 15, 22 28-day cycle	13.0	1st year 0 (cycle 1 - 2) 2 (cycle 3 - 6) 3 (from cycle 7)	1st year 29.0[4]
Prednisolone				
Prednisolone	incalculable			
Prednisone				
Prednisone	incalculable			
Best supportive care				
Best supportive care	Different from patient to patient			

Consumption:

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body height: 1.72 m; average body weight: 77 kg). This results in a body surface area of 1.90 m² (calculated according to Du Bois 1916)[5].

[5] Federal Health Reporting. Average body measurements of the population (2017, both sexes), www.gbe-bund.de

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Melphalan flufenamide in combination with dexamethasone					
Melphalan flufenamide	40 mg	40 mg	2 x 20 mg	13.0	26 x 20 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	52.0	52 x 40 mg
Appropriate comparator therapy					
Bortezomib monotherapy					
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	32.0	32 x 2.5 mg
Bortezomib in combination with pegylated liposomal doxorubicin					
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	32.0	32 x 2.5 mg
Doxorubicin (pegylated, lysosomal)	30 mg/m²	57 mg	1 x 20 mg 1 x 50 mg	8.0	8 x 20 mg 8 x 50 mg
Bortezomib in combination with dexamethasone					
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	16.0 - 32.0	16 - 32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	32.0 - 64.0	32 - 64 x 20 mg
Carfilzomib in combination with lenalidomide and dexamethasone					
Carfilzomib	1st cycle day 1, 2 20 mg/m² Thereafter 27 mg/m²	1st cycle day 1, 2 38 mg Thereafter 51.3 mg	1st cycle Day 1, 2 1 x 10 mg + 1 x 30 mg Thereafter 1 x 60 mg	1st year 76.0	1st year 2 x 10 mg + 2 x 30 mg + 74 x 60 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273.0	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	52.0	52 x 40 mg
Carfilzomib in combination with dexamethasone					
Carfilzomib	1st cycle day 1, 2 20 mg/m²	1st cycle day 1, 2 38 mg	1st cycle day 1, 2 1 x 10 mg + 1 x 30 mg	78.0	1st year 154 x 10 mg + 78 x 30 mg + 76 x 60 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	Thereafter 56 mg/m²	Thereafter 106.4 mg	Thereafter 2 x 10 mg + 1 x 30 mg + 1 x 60 mg		
Dexamethasone	20 mg	20 mg	1 x 20 mg	104.0	104 x 20 mg
Daratumumab in combination with lenalidomide and dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	1st year: 23.0	1st year: 23 x 1,800 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273.0	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	1st year: 29.0	1st year: 29 x 40 mg
Daratumumab in combination with bortezomib and dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	1st year: 21.0	1st year: 21 x 1,800 mg
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	32.0	32 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	53.0	53 x 20 mg
Daratumumab monotherapy (only for subjects with disease progression on last therapy)					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	1st year: 23.0	1st year: 23 x 1,800 mg
Elotuzumab in combination with lenalidomide and dexamethasone					
Elotuzumab	10 mg/kg	770 mg	2 x 400 mg	1st year: 30.0	1st year: 60 x 400 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273.0	273 x 25 mg
Dexamethasone	1st - 2nd cycle Day 1, 8, 15, 22 28 mg From 3rd cycle Day 1, 15 28 mg Day 8, 22 40 mg	1st - 2nd cycle Day 1, 8, 15, 22 28 mg From 3rd cycle Day 1, 15 28 mg Day 8, 22 40 mg	1 x 8 mg + 1 x 20 mg or 1 x 40 mg	52.0	1st year 30 x 8 mg + 30 x 20 mg + 22 x 40 mg
Elotuzumab + pomalidomide + dexamethasone (only for subjects with disease progression on last therapy)					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Elotuzumab	1st - 2nd cycle Day 1, 8, 15, 22 10 mg/kg From 3rd cycle Day 1 20 mg/kg	1st - 2nd cycle Day 1, 8, 15, 22 770 mg From 3rd cycle Day 1 1540 mg	1st - 2nd cycle Day 1, 8, 15, 22 2 x 400 mg From 3rd cycle Day 1 4 x 400 mg	1st year: 19.0	1st year: 60 x 400 mg
Pomalidomide	4 mg	4 mg	1 x 4 mg	273.0	273 x 4 mg
Dexamethasone	1st - 2nd cycle Day 1, 8, 15, 22 28 mg From 3rd cycle Day 1 28 mg Day 8, 15, 22 40 mg	1st - 2nd cycle Day 1, 8, 15, 22 28 mg From 3rd cycle Day 1 28 mg Day 8, 15, 22 40 mg	1 x 8 mg + 1 x 20 mg or 1 x 40 mg	52.0	1st year 19 x 8 mg + 19 x 20 mg + 33 x 40 mg
Isatuximab in combination with pomalidomide and dexamethasone (only for subjects with disease progression on last therapy)					
Isatuximab	10 mg/kg	770 mg	1 x 500 mg + 3 x 100 mg	28.0	1st year: 28 x 500 mg + 84 x 100 mg
Pomalidomide	4 mg	4 mg	1 x 4 mg	273.0	273 x 4 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	24.0	24 x 40 mg
Ixazomib in combination with lenalidomide and dexamethasone					
Ixazomib	4 mg	4 mg	1 x 4 mg	39.0	39 x 4 mg
Lenalidomide	25 mg	25 mg	1 x 25 mg	273.0	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	52.0	52 x 40 mg
Lenalidomide in combination with dexamethasone					
Lenalidomide	25 mg	25 mg	1 x 25 mg	273.0	273 x 25 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	1st year:	1st year:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
				84.0	84 x 40 mg
Panobinostat in combination with bortezomib and dexamethasone					
Panobinostat	20 mg	20 mg	1 x 20 mg	48.0 - 96.0	48 x 20 mg - 96 x 20 mg
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	32.0 - 48.0	32 x 2.5 mg - 48 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	64.0 - 96.0	64 x 20 mg - 96 x 20 mg
Pomalidomide in combination with bortezomib and dexamethasone					
Pomalidomide	4 mg	4 mg	1 x 4 mg	243.6	243.6 x 4 mg
Bortezomib	1.3 mg/m²	2.47 mg	1 x 2.5 mg	50.8	50.8 x 2.5 mg
Dexamethasone	20 mg	20 mg	1 x 20 mg	101.6	101.6 x 20 mg
Pomalidomide in combination with dexamethasone (only for subjects with disease progression on last therapy)					
Pomalidomide	4 mg	4 mg	1 x 4 mg	273.0	273 x 4 mg
Dexamethasone	40 mg	40 mg	1 x 40 mg	52.0	52 x 40 mg
Cyclophosphamide (in combination with other antineoplastic medicinal products)[6]					
Cyclophosphamide	400 mg/m²	760 mg	1 x 1,000 mg	10.4	10.4 x 1,000 mg
Melphalan	8 mg/m²	15.2 mg	8 x 2 mg	41.6	332.8 x 2 mg
Carmustine	20 mg/m²	38 mg	1 x 100 mg	10.4	10.4 x 100 mg
Vincristine [8]	1.2 mg/m²	2 mg	1 x 2 mg	10.4	10.4 x 2 mg
Prednisone	1st - 3rd cycle Day 1 - 7 40 mg/m² Day 8 - 14 20 mg/m² From 4th cycle Day 1 - 7	1st - 3rd cycle Day 1 - 7 76 mg Day 8 - 14 38 mg From 4th cycle Day 1 - 7 76 mg	1 x 50 mg 1 x 20 mg 1 x 10 mg or 2 x 20 mg	93.8	1st year 72.8 x 50 mg 114.8 x 20 mg 72.8 x 10 mg

[6] Oken MM, Harrington DP, Abramson N et al, Comparison of melphalan and prednisone with vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of multiple myeloma. Cancer 1997; 79(8): 1561-1567.
https://acsjournals.onlinelibrary.wiley.com/doi/full/10.1002/%28SICI%291097-0142%2819970415%2979%3A8%3C1561%3A%3AAID-CNCR18%3E3.0.CO%3B2-W

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	40 mg/m²				
Melphalan					
Melphalan	0.4 mg/kg	30.8 mg	1 x 50 mg	13.0	13.0 x 50 mg
Doxorubicin					
Doxorubicin[7]	60 mg/m² - 75 mg/m²	114 mg - 142.5 mg	1 x 150 mg	6.0 - 9.0	6.0 x 150 mg - 9.0 x 150 mg
Carmustine (in combination with other cytostatic agents and a corticosteroid, especially prednisone) [6]					
Carmustine	20 mg/m²	38 mg	1 x 100 mg	10.4	10.4 x 100 mg
Cyclophosphamide	400 mg/m²	760 mg	1 x 1,000 mg	10.4	10.4 x 1,000 mg
Melphalan	8 mg/m²	15.2 mg	8 x 2 mg	41.6	332.8 x 2 mg
Vincristine [8]	1.2 mg/m²	2 mg	1 x 2 mg	10.4	10.4 x 2 mg
Prednisone	1st - 3rd cycle Day 1 - 7 40 mg/m² Day 8 - 14 20 mg/m² From 4th cycle Day 1 - 7 40 mg/m²	1st - 3rd cycle Day 1 - 7 76 mg Day 8 - 14 38 mg From 4th cycle Day 1 - 7 76 mg	1 x 50 mg 1 x 20 mg 1 x 10 mg or 2 x 20 mg	93.8	1st year 72.8 x 50 mg 114.8 x 20 mg 72.8 x 10 mg
Vincristine					
Vincristine[8]	1.4 mg/m²	2 mg	1 x 2 mg	52.1	52.1 x 2 mg
Dexamethasone monotherapy					
Dexamethasone[3]	40 mg	40 mg	5 x 8 mg	156.0	780.0 x 8 mg
Daratumumab in combination with pomalidomide and dexamethasone					
Daratumumab	1,800 mg	1,800 mg	1 x 1,800 mg	1st year: 23.0	1st year: 23 x 1,800 mg
Pomalidomide	4 mg	4 mg	1 x 4 mg	273.0	273 x 4 mg

[7] Recommended maximum cumulative dose according to the product information: 450 - 550 mg/m²
[8] The single dose should not exceed 2 mg according to the product information of vincristine

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment day	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Dexamethasone	40 mg	40 mg	1 x 40 mg	1st year: 29.0	1st year: 29 x 40 mg
Prednisolone					
Prednisolone	incalculable				
Prednisone					
Prednisone	incalculable				
Best supportive care					
Best supportive care	Different from patient to patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Melphalan flufenamide 20 mg	20 PIC	€ 6,737.68	€ 2.00	€ 654.00	€ 6,081.68
Dexamethasone 40 mg[9]	50 Pic	€ 188.00	€ 2.00	€ 0.00	€ 186.00
Appropriate comparator therapy					
Bortezomib 2.5 mg	1 Pic	€ 185.33	€ 2.00	€ 8.26	€ 175.07
Pegylated liposomal doxorubicin 20 mg	1 Pic	€ 721.45	€ 2.00	€ 89.87	€ 629.58
Pegylated liposomal doxorubicin 50 mg	1 Pic	€ 1,778.86	€ 2.00	€ 224.69	€ 1,552.17
Dexamethasone 20 mg[9]	20 Pic	€ 54.05	€ 2.00	€ 0.00	€ 52.05
Dexamethasone 20 mg[9]	50 Pic	€ 118.85	€ 2.00	€ 0.00	€ 116.85

[9] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Carfilzomib 10 mg	1 Pic	€ 196.99	€ 2.00	€ 17.63	€ 177.36
Carfilzomib 30 mg	1 Pic	€ 568.39	€ 2.00	€ 52.88	€ 513.51
Carfilzomib 60 mg	1 Pic	€ 1,125.50	€ 2.00	€ 105.75	€ 1,017.75
Lenalidomide 25 mg	21 Pic	€ 64.12	€ 2.00	€ 2.51	€ 59.61
Dexamethasone 40 mg[9]	50 Pic	€ 188.00	€ 2.00	€ 0.00	€ 186.00
Daratumumab 1,800 mg	1 Pic	€ 5,809.83	€ 2.00	€ 234.65	€ 5,573.18
Dexamethasone 20 mg[9]	10 Pic	€ 32.38	€ 2.00	€ 0.00	€ 30.38
Elotuzumab 400 mg	1 PIC	€ 1,557.88	€ 2.00	€ 146.88	€ 1,409.00
Dexamethasone 8 mg[9]	100 Pic	€ 123.37	€ 2.00	€ 8.87	€ 112.50
Pomalidomide 4 mg [9]	21 Pic	€ 9,061.45	€ 2.00	€ 886.12	€ 8,173.33
Isatuximab 100 mg	1 Pic	€ 368.71	€ 2.00	€ 33.92	€ 332.79
Isatuximab 500 mg	1 Pic	€ 1,790.14	€ 2.00	€ 169.62	€ 1,618.52
Ixazomib 4 mg	3 Pic	€ 6,431.26	€ 2.00	€ 624.00	€ 5,805.26
Panobinostat 20 mg	6 Pic	€ 4,656.37	€ 2.00	€ 450.23	€ 4,204.14
Cyclophosphamide 1000 mg	6 Pic	€ 127.41	€ 2.00	€ 11.02	€ 114.39
Melphalan 2 mg	50 Pic	€ 56.20	€ 2.00	€ 4.26	€ 49.94
Carmustine 100 mg	1 Pic	€ 3,842.58	€ 2.00	€ 185.28	€ 3,655.30
Prednisone 50 mg [9]	50 Pic	€ 68.02	€ 2.00	€ 4.49	€ 61.53
Prednisone 20 mg [9]	100 Pic	€ 29.25	€ 2.00	€ 1.42	€ 25.83
Prednisone 10 mg [9]	100 Pic	€ 21.19	€ 2.00	€ 0.78	€ 18.41
Vincristine 2 mg	1 Pic	€ 37.63	€ 2.00	€ 1.25	€ 34.38
Melphalan 50 mg	1 Pic	€ 52.29	€ 2.00	€ 3.89	€ 46.40
Doxorubicin 150 mg[9]	1 Pic	€ 418.32	€ 2.00	€ 0.00	€ 416.32
Prednisolone	incalculable				
Prednisone	incalculable				
Abbreviations: HC = hard capsules; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PSI = powder for solution for injection, PIC = powder for the preparation of an infusion solution concentrate; TAB = tablets PIS = powder for the preparation of an infusion solution, CIS = concentrate for the preparation of an infusion solution, FCT = film-coated tablets, PSS = powder and solvent for the preparation of an infusion solution, DDS = dry substance with solvent					

LAUER-TAXE® last revised: 1 March 2023

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations

(e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Type of service	Cost per pack	Costs after deduction of statutory rebates	Costs per service[10]	Treatment days per year	Costs/ patient/ year
Appropriate comparator therapy					
Daratumumab *in combination with lenalidomide and dexamethasone*					
Premedication[11]					
Dexamethasone 40 mg, oral	€ 188.00[9] 50 x 40 mg	€ 186.00 [€ 2.00; € 0.00]	€ 3.72	1st year 23	1st year € 85.56
Paracetamol[12] 500 - 1,000 mg, oral	€ 3.47 20 x 500 mg € 3.32 10 x 1,000 mg	€ 3.15 [€ 0.17; € 0.15] € 3.01 [€ 0.17; € 0.14]	€ 0.16 - € 0.30	1st year 23	1st year € 3.62 - € 6.92
Dimetindene 1 mg/10 kg BW, IV	€ 23.67 5 x 4 mg	€ 15.86 [€ 2.00; € 5.81]	€ 6.34	1st year 23	1st year € 145.91
Daratumumab *in combination with bortezomib and dexamethasone*					
Premedication[11]					
Dexamethasone 20 mg, oral	€ 118.85[9] 50 x 20 mg	€ 116.85 [€ 2.00; € 0.00]	€ 2.34	1st year 21	1st year € 49.08
Paracetamol[12] 500 - 1,000 mg, oral	€ 3.47 20 x 500 mg € 3.32 10 x 1,000 mg	€ 3.15 [€ 0.17; € 0.15] € 3.01 [€ 0.17; € 0.14]	€ 0.16 - € 0.30	1st year 21	1st year € 3.31 - € 6.32

[10] Proportionate share of cost per pack for consumption per treatment day. Rounded interim result.

[11] According to the product information for Darzalex (last revised: January 2022)

[12] Fixed reimbursement rate. Non-prescription medicinal products that are reimbursable at the expense of the statutory health insurance according to Section 12, paragraph 7, of the AM-RL (information as concomitant medication in the product information of the prescription medicinal product) are not subject to the current medicinal products price regulation. Instead, in accordance with Section 129 paragraph 5a SGB V, when a non-prescription medicinal product is dispensed invoiced according Section 300, a medicinal product sale price applies to the insured person in the amount of the sale price of the pharmaceutical company plus the surcharges according to Sections 2 and 3 of the Pharmaceutical Price Ordinance in the valid version of 31 December 2003.

Type of service	Cost per pack	Costs after deduction of statutory rebates	Costs per service[10]	Treatment days per year	Costs/ patient/ year
Dimetindene 1 mg/10 kg BW, IV	€ 23.67 5 x 4 mg	€ 15.86 [€ 2.00; € 5.81]	€ 6.34	1st year 21	1st year € 133.22
Elotuzumab *in combination with lenalidomide and dexamethasone*					
Premedication[13]					
Dexamethasone 8 mg, IV	€ 20.35[9] 10 x 8 mg	€ 17.63 [€ 2.00; € 0.72]	€ 1.76	1st year 30	1. year € 52.89
Dimetindene 1 mg/10 kg BW, IV	€ 23.67 5 x 4 mg	€ 15.86 [€ 2.00; € 5.81]	€ 6.34	1st year 30	1st year € 190.32
Famotidine 20 mg, oral	€ 20.15[9] 100 x 20 mg	€ 17.45 [€ 2.00; € 0.70]	€ 0.17	1st year 30	1st year € 5.24
Paracetamol[12] 500 - 1,000 mg, oral	€ 3.47 20 x 500 mg € 3.32 10 x 1,000 mg	€ 3.15 [€ 0.17; € 0.15] € 3.01 [€ 0.17; € 0.14]	€ 0.16 - € 0.30	1st year 30	1st year € 4.73 - € 9.03 -
Elotuzumab + pomalidomide + dexamethasone (only for subjects with disease progression on last therapy)					
Premedication					
Dexamethasone 8 mg, IV	€ 20.35[9] 10 x 8 mg	€ 17.63 [€ 2.00; € 0.72]	€ 1.76	1st year 19	1st year € 33.50
Dimetindene 1 mg/10 kg BW, IV	€ 23.67 5 x 4 mg	€ 15.86 [€ 2.00; € 5.81]	€ 6.34	1st year 19	1st year € 120.54
Famotidine 20 mg, oral	€ 23.67 5 x 4 mg	€ 15.86 [€ 2.00; € 5.81]	€ 6.34	1st year 19	1st year € 3.32
Paracetamol[12] 500 - 1,000 mg, oral	€ 3.47 20 x 500 mg € 3.32 10 x 1,000 mg	€ 3.15 [€ 0.17; € 0.15] € 3.01 [€ 0.17; € 0.14]	€ 0.16 - € 0.30	1st year 19	1st year € 2.99 - € 5.72

[13] According to the product information for Empliciti (last revised: February 2022)

Type of service	Cost per pack	Costs after deduction of statutory rebates	Costs per service[10]	Treatment days per year	Costs/ patient/ year
Daratumumab *monotherapy*					
Premedication[11]					
Methylprednisolone 60 mg - 100 mg, IV	€ 21.31 3 x 32 mg	€ 16.32 [€ 2.00; € 2.99]	€ 5.44	1st year 23	1st year € 250.24 - € 500.48
Postmedication[11]					
Methylprednisolone 20 mg, oral	€ 73.80[9] 100 x 16 mg € 29.31[9] 100 x 4 mg	€ 66.86 [€ 2.00; € 4.94] € 25.88 [€ 2.00; € 1.43]	€ 0.93	1st year 46	1st year € 42.66
Daratumumab in combination with pomalidomide and dexamethasone					
Premedication[11]					
Dexamethasone 40 mg, oral	€ 188.00[9] 50 x 40 mg	€ 186.00 [€ 2.00; € 0.00]	€ 3.72	1st year 23	1st year € 85.56
Paracetamol[12] 500 - 1,000 mg, oral	€ 3.47 20 x 500 mg € 3.32 10 x 1,000 mg	€ 3.15 [€ 0.17; € 0.15] € 3.01 [€ 0.17; € 0.14]	€ 0.16 - € 0.30	1st year 23	1st year € 3.62 - € 6.92
Dimetindene 1 mg/10 kg BW, IV	€ 23.67 5 x 4 mg	€ 15.86 [€ 2.00; € 5.81]	€ 6.34	1st year 23	1st year € 145.91

Patients receiving therapy with carfilzomib, pomalidomide, daratumumab and lenalidomide should be tested for the presence of HBV infection before initiating the respective treatment. For the diagnosis of suspected chronic hepatitis B, sensibly coordinated steps are required[14]. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. If HBs antigen is positive, an active HBV infection is detected.

In deviation from this, additional required SHI services are required for the diagnosis of suspected chronic hepatitis B, which usually differ between the medicinal product to be

[14] S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011" https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf

evaluated and the appropriate comparator therapy and are consequently considered as additionally required SHI services in the resolution.

Designation of the therapy	Designation of the service	Number	Cost per unit	Costs/ patient/ year
Appropriate comparator therapy				
Carfilzomib Daratumumab Lenalidomide Pomalidomide	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)	1	€ 89.50	€ 89.50

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Melphalan Flufenamide

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 24 August 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 27 September 2022.

On 30 September 2022, the pharmaceutical company submitted a dossier for the benefit assessment of melphalan flufenamide to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 4 October 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient melphalan flufenamide.

The dossier assessment by the IQWiG was submitted to the G-BA on 23 December 2022, and the written statement procedure was initiated with publication on the G-BA website on 2 January 2023. The deadline for submitting written statements was 23 January 2023.

The oral hearing was held on 6 February 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 March 2023, and the proposed resolution was approved.

At its session on 16 March 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 August 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	27 September 2022	New implementation of the appropriate comparator therapy
Working group Section 35a	31 January 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	6 February 2023	Conduct of the oral hearing
Working group Section 35a	14 February 2023 28 February 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	7 March 2023	Concluding discussion of the draft resolution
Plenum	16 March 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 March 2023

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken